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RESPIRATORY ADAPTATIONS IN ACID-BASE DISTURBANCES: ROLE OF CERE--ETC(U)
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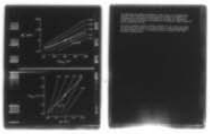

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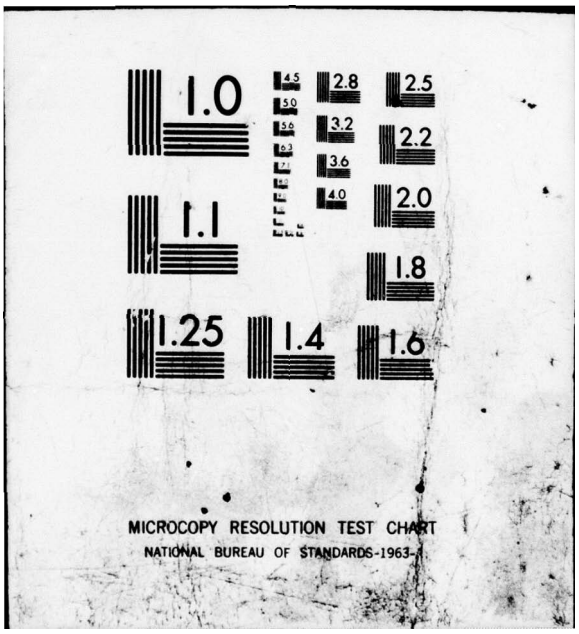
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1. REPORT NUMBER: M-16/79 (6)	2. GOVT ACCESSION NO.
3. RECIPIENT'S CATALOG NUMBER	
4. TITLE (and Subtitle): Respiratory Adaptations in Acid-base Disturbances: Role of Cerebral Fluids (1)	5. TYPE OF REPORT & PERIOD COVERED
6. PERFORMING ORG. REPORT NUMBER	
7. AUTHOR(s): (10) V. Fencl and R. A. Gabel	8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS: US Army Research Institute of Environmental Medicine, Natick, MA 01760	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 6.11.01.A (16) 3A161101A91C 94181022
11. CONTROLLING OFFICE NAME AND ADDRESS: US Army Medical Research & Development Command, Fort Detrick, Frederick, MD 21701	12. REPORT DATE: (11) 19 Jun 79 13. NUMBER OF PAGES: 11
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office): Same as above	15. SECURITY CLASS. (of this report): unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

LEVEL II

16. DISTRIBUTION STATEMENT (of this Report)

Distribution of this document is unlimited. (12) 13p.

DDC AUG 29 1979 C

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

N/A

18. SUPPLEMENTARY NOTES

N/A

19. KEY WORDS (Continue on reverse side if necessary and identify by block number): acid-base balance/regulation of breathing/cerebrospinal fluid/cerebral interstitial fluid/blood-brain barrier

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number): The "respiratory" (Pa_{CO_2}) and "metabolic" (~~Base Excess~~, $\pm BE$) components of acid-base homeostasis are defined. A quantitative empirical description of the (incomplete) mutual compensations in steady acid-base disturbances primarily occurring in either of the two components is presented, based upon data compiled from the literature. Respiratory adaptations in steady acid-base disturbances of metabolic origin (hyperventilation with hypocapnia in primary metabolic acidosis, and hypoventilation with hypercapnia in metabolic alkalosis) are analyzed as a function of the

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acidity of the cerebral fluids (cerebrospinal and cerebral interstitial fluid).

Respiratory Adaptations in Acid-base Disturbances: Role of Cerebral Fluids

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Running Title: Cerebral Fluids in Respiratory Adaptations

Key Words: Acid-base Balance/Regulation of Breathing/Cerebrospinal Fluid/Cerebral Interstitial Fluid/Blood-brain Barrier

Abstract: The "respiratory" (Pa_{CO_2}) and "metabolic" (Base Excess, ±BE) components of acid-base homeostasis are defined. A quantitative empirical description of the (incomplete) mutual compensations in steady acid-base disturbances primarily occurring in either of the two components is presented, based upon data compiled from the literature. Respiratory adaptations in steady acid-base disturbances of metabolic origin (hyperventilation with hypocapnia in primary metabolic acidosis, and hypoventilation with hypercapnia in metabolic alkalosis) are analyzed as a function of the acidity of the cerebral fluids (cerebrospinal and cerebral interstitial fluid).

Acid-base balance is an integrated homeostatic system in which two "independent variables"[1] are used by the controller: P_{CO_2} in arterial blood--the "respiratory component"--and the "strong-ion difference" ([S.I.D.], the difference between the sums of the fully dissociated cations and anions in blood plasma) for the "non-respiratory" or "metabolic component" [19]. Deviations from the normal value of [S.I.D.] (about 42 mM/l) are reflected as base excess (-BE, mM/l) or base deficit (-BE, mM/l) [18]. The normal acid-base balance in a resting person, breathing air at normal barometric pressure is characterized by Pa_{CO_2} = 40 torr (5.33 kPa), and BE = 0 ([S.I.D.] = 42 mM/l), pH being 7.40. Primary disturbances in the "metabolic" ("non-respiratory") component are characterized by changes in BE: +BE (increase in [S.I.D.]) is metabolic alkalosis, and -BE (decrease in [S.I.D.]) is metabolic acidosis. The value of Pa_{CO_2}, at a given CO_2 production ($\dot{V}_{CO_2}$, l/min), is inversely proportional to the effective alveolar ventilation ($\dot{V}_A$, l/min):

Footnote[1]

An "independent variable" is one that can be changed from outside of the system; change in one independent variable does not affect the value of another independent variable. "Dependent variables" in the acid-base balance in body fluids are e.g. $[H^+]$, $[OH^-]$, $[HCO_3^-]$, dissociation of weak electrolytes ("buffers"). The "dependent variables" can only change (all simultaneously) as a function of changes in one or more of the independent variables [19].

$$Pa_{CO_2} = K \dot{V}_{CO_2}/\dot{V}_A. \quad (1)$$

Deviation from the normal Pa_{CO_2} is a consequence of change in pulmonary ventilation. Thus, the regulation of breathing, through its effect on Pa_{CO_2}, is an integral part of the acid-base homeostatic system.

When primary disturbances in acid-base balance occur, a mutual compensation develops within hours, and is fully established within a few days: primary disturbances in the "respiratory" component are compensated by an opposite deviation in the "metabolic" component, and vice versa. Primary respiratory acidosis (chronic CO_2 retention) is compensated for by renal production of +BE, and with primary respiratory alkalosis (chronic hypocapnia, as e.g. in adaptation to high altitude) a -BE is produced. In an analogous way, primary metabolic alkalosis or acidosis induces compensatory hypercapnia or hypocapnia, respectively. Figures 1 and 2, constructed from published data, describe the observed quantitative interactions between the "respiratory" and "metabolic" components of acid-base regulation in humans. In primary disturbances of "respiratory" origin (Figure 1), BE changes as a function of Pa_{CO_2}. Over the range of Pa_{CO_2} values of 20 to 60 torr (2.67 to 8.00 kPa), the plot fits a straight line:

$$BE\ (mM/l) = 0.34\ Pa_{CO_2}\ (torr) - 14 \quad (2)$$

Thus, for instance, when Pa_{CO_2} is increased from its normal value of 40 torr (5.33 kPa) to 50 torr (6.67 kPa), BE increases from 0 to 3.4 mM/l. This renal compensation for a primary respiratory acid-base disturbance is not complete, as indicated by the plot of "iso-pH" lines in Figure 1. In primary disturbances of "metabolic" origin (Figure 2), Pa_{CO_2}

changes as a function of primary deviations in BE. Over the range of BE -20 to +20 mM/l ([S.I.D.] approximately 22 - 62 mM/l), the plot fits a straight line:

$$Pa_{CO_2}\ (torr) = BE\ (mM/l) + 40 \qquad (3)$$

Thus, for instance, BE of +10 mM/l produces an increase in P_{CO_2} to 40 + 10 = 50 torr (6.67 kPa), and BE of -10 mM/l elicits a Pa_{CO_2} value of -10 + 40 = 30 torr (4.00 kPa). Again, as seen from the "iso-pH" lines in Figure 2, the respiratory compensation for primary metabolic acid-base disturbances is incomplete.

Mechanisms responsible for these mutual compensations in the two types of primary acid-base disturbances have not been fully clarified. We shall not comment on the renal mechanisms that produce base excess or base deficit in response to chronic hypercapnia or hypocapnia (Figure 1), but shall concentrate on the respiratory adaptations that follow the primary disturbances of "metabolic" origin, as empirically described in Figure 2.

Changes in the resting pulmonary ventilation (with reciprocal changes in Pa_{CO_2}, Equation 1) that occur in metabolic acidosis and alkalosis cannot be readily explained by chemical respiratory stimuli identifiable in arterial blood. In stable metabolic acidosis with established respiratory compensation, Pa_{CO_2} is abnormally low and the prevailing arterial-blood pH is not acidotic enough to account for the hyperventilation [6] [7] [14]. Analogous reasoning pertains to metabolic alkalosis. It appears that it is a change in $[H^+]$ in cerebral fluids (cerebrospinal fluid, CSF; and cerebral interstitial fluid, cISF), detected by the

"central chemoreceptors" in the medulla oblongata [13] [16], that provides a significant stimulus for resetting the resting pulmonary ventilation in response to metabolic acidosis or alkalosis. Following the pioneering work of LEUSEN [11], it has been shown that the resting $\dot{V}_A$ (and its reciprocal function, the arterial-blood P_{CO_2}) is proportional to the $[H^+]$ in cerebral fluids [2] [3] [6] [7]. These fluids are separated from blood by the blood-brain barrier, and their ionic composition is different from that of the ultrafiltrate of blood plasma. As a result of the (poorly understood) functioning of the blood brain barrier, changes in [S.I.D.] (or BE) that occur in blood plasma during metabolic acidosis or alkalosis are attenuated in the ionic composition of the cerebral fluids [12].

The "central chemoreceptors" appear to be located at some distance from the ventro-lateral surface of the medulla, exposed to cISF and not to the cisternal CSF [2] [3] [15]. However, in the normal acid-base balance and during steady metabolic acidosis or alkalosis at normal barometric pressure, the ionic composition (including $[H^+]$) of cISF and CSF are the same [6]; thus, the variable "centrogenic respiratory drive" contributing to the respiratory adaptation in steady "metabolic" acid-base disturbances can be identified, and measured, as the $[H^+]$ in cisternal CSF.

Respiratory adaptations to prolonged stable metabolic acidosis or alkalosis, by inducing changes in P_{CO_2} in alveolar gas, arterial blood and other body fluids, together with the blood-brain barrier, which attenuates the reflection in cerebral fluids of the changes in [S.I.D.]

existing in blood plasma, serve to reduce the variation of $[H^+]$ in the cerebral extracellular fluids to a small fraction of that occurring in blood [7].

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Fig. 1. Changes in base excess and base deficit (±BE) observed in stable acid-base disturbances of purely respiratory origin. The heavy line is least-squares regression of BE as a function of primary changes in Pa_{CO_2}. The slope (λ) indicates that BE changes by 0.34 mM/l with a primary change in Pa_{CO_2} of 1 torr. The thin lines are "iso-pH" lines of the plot of BE vs Pa_{CO_2} in blood: the renal compensation for respiratory alkalosis and acidosis is incomplete. Based on data compiled from references [4] [5] [8] [10] [17] [20] [21].

Fig. 2. Changes in Pa_{CO_2} observed in stable acid-base disturbances of "metabolic" origin. The heavy line is least-squares regression of Pa_{CO_2} as a function of primary changes in base excess and base deficit (±BE). The slope (λ) indicates that Pa_{CO_2} changes by 1 torr with primary change in BE of 1 mM/l. Comparison with the slopes of the thin "iso-pH" lines shows that the respiratory compensation of stable metabolic acidosis and alkalosis is incomplete. Based on data compiled from references [1] [7] [9] [21].

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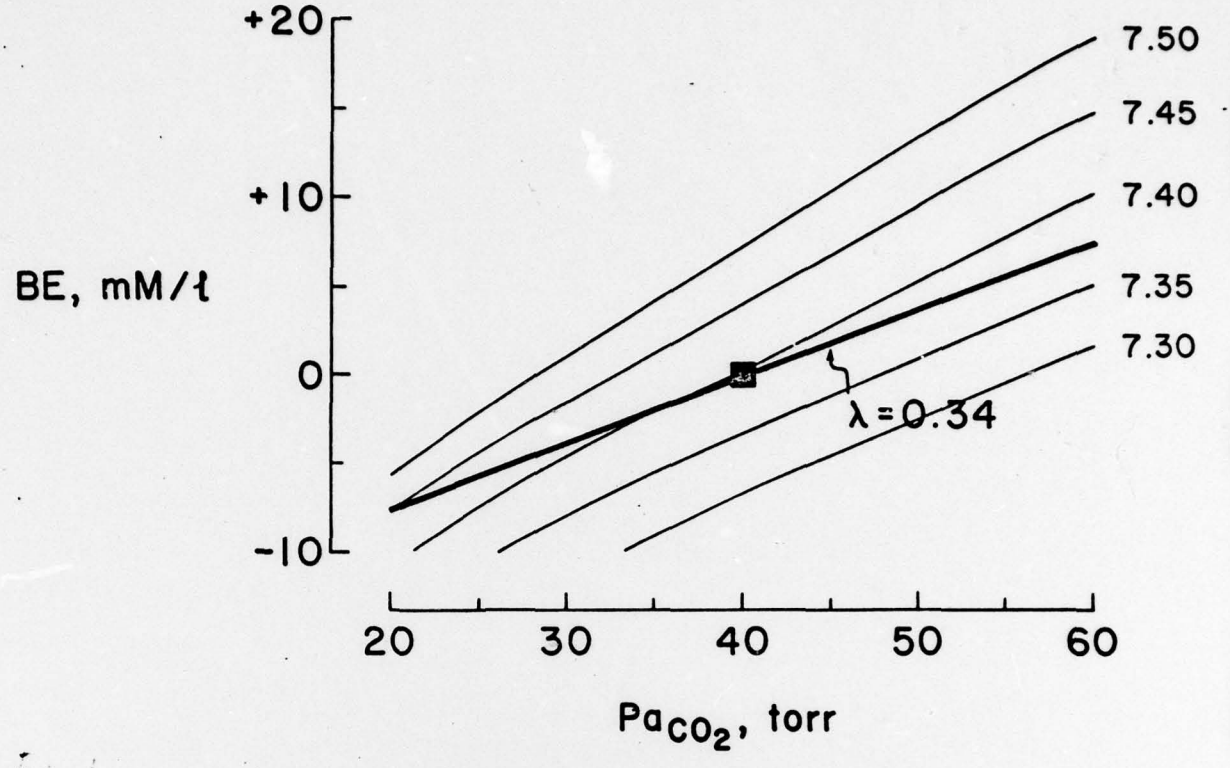
+20
+10
0
-10
BE, mM/l
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7.40
7.35
7.30
λ=0.34
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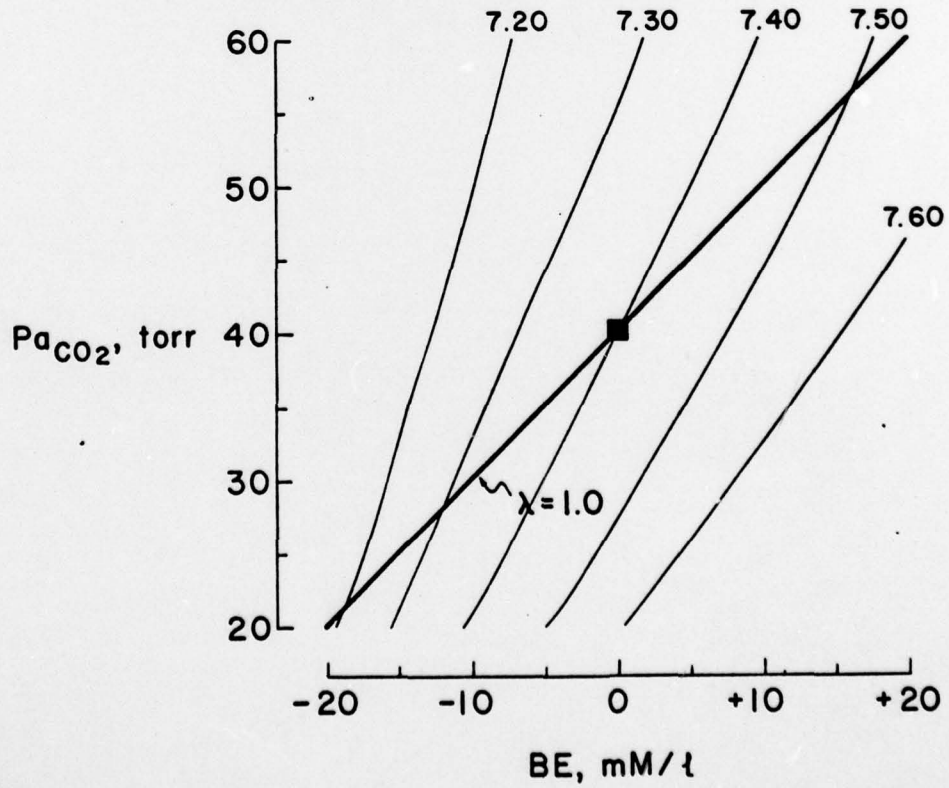
30
40
50
60
Pa$_{CO_2}$, torr

Fig. 1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50
40
30
20
Pa$_{CO_2}$, torr
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7.30
7.40
7.50
7.60
λ=1.0
-20
-10
0
+10
+20
BE, mM/l

Fig. 2

In conducting the research described in this report, the investigators adhered to the 'Guide for the Care and Use of Laboratory Animals,' as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council.

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